12. (amended) The method of claim 11 wherein the amplified oligonucleotide of said epitope detector from step (c) is detected via contacting the amplified oligonucleotide of said epitope detector from step (c) with a fluorescent dye or probe which stains the oligonucleotide and measuring fluorescence emitted from the stained oligonucleotide which is indicative of epitope detector bound to the surface and molecules expressing the selected epitope in the sample.

13. The method of claim 11 further comprising quantifying the amplified oligonucleotide of said epitope detector from step (c) and detected in step (e).

REMARKS

Claims 1 through 14 are pending in the instant application. Claim 2 through 10 have been withdrawn from consideration by the Examiner. Claims 1 and 11-14 have been rejected. Claims 1, 11, 12 and 13 have been amended. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Restriction Requirement

The Examiner has restricted the claims as follows:

Group I, claims 1 and 14, drawn to a method for detecting molecule expressing a selected epitope in a sample, classified in class 435, subclass 91.2;

Group II, claims 2-3 and 5-6, drawn to a kit for the detection of molecules expressing a selected epitope via fluorescence and for profiling proteins in a cell lysate, classified in class 435, subclass 810;

Group III, claim 4, drawn to a method for profiling proteins in a cell lysate, classified in class 435, subclass 92.51;

Group IV, claims 7-8, drawn to a method for developing a two-component system in vitro, classified in class 435, subclass 91.5; and

Group V, claims 9-10, drawn to a method for interacting of molecules in vitro, classified in class 435, subclass 91.5.

The Examiner suggests that these Groups are distinct. Specifically, with respect to Groups II and I, III and IV, the Examiner acknowledges their relationship as product and process of use, but suggests that the product of Group II can be used in the materially different process of immunoassay. With respect to Groups I, III, IV, and V, the Examiner suggest that the methods

are unrelated and patentably distinct based upon the different functions of the preamble and the different method steps involved to perform the method.

Applicants respectfully traverse this Restriction Requirement.

In order for a restriction requirement to be proper, two criteria must be met (MPEP 803). First, the inventions must be independent and distinct as claimed. Second, there must be a serious burden on the Examiner if the invention is not restricted. Clearly, a proper search of the method of Group I, would also reveal any art relating to kits for use of this methods and uses for the method as set forth in Groups II-V. Therefore, there would not be a serious burden on the Examiner if this restriction were not made. Accordingly, this restriction requirement does not meet both criteria as set forth in MPEP § 803 to be proper and withdrawal is respectfully requested.

However, in an earnest effort to be completely responsive, Applicants elect to prosecute Group I, claims 1 and 11-14, with traverse.

II. Objection to Specification

The Examiner has objected to the title as not being

descriptive because it is directed to a method for immuno-detection of epitopes on molecules and for detection of interactions of molecules via fluorescent dyes, while the claim language is directed to a method of detecting molecules expressing a selected epitope via fluorescent dyes. Thus, in accordance with the Examiner's suggestion, Applicants are providing a new title more clearly indicative of the invention to which the claims are directed.

III. Rejection of Claims 11-14 under 35 U.S.C. § 112, second paragraph

Claims 11-14 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner suggests that claims 11-14 are vague and indefinite because the language "the amplified oligonucleotide" in step (d) of claim 11 has no antecedent basis. Accordingly, in an earnest effort to advance the prosecution of this case, claims 11, 12 and 13 have been amended to clarify that the amplified oligonucleotide is that of said epitope detector from step (c). Withdrawal of this

rejection is respectfully requested in light of the amendments to the claims.

IV. Rejection of Claim 1 under 35 U.S.C. § 102(b)

Claim 1 has been rejected under 35 U.S.C. § 102(b) as being anticipated by Suzuki et al. (Jpn. J. Cancer Res. Vol. 86 pg 885-559). The Examiner suggests that Suzuki et al. disclose a method for detecting molecules expressing a selected epitope in a sample which comprises: immobilizing a molecule expressing a selected epitope in a sample to a selected surface; contacting the surface with an epitope detector comprising an oligonucleotide attached to a monoclonal antibody for the selected epitope; amplifying the oligonucleotide of the epitope detector; contacting the amplified oligonucleotide with a fluorescent dye which stains the oligonucleotide; and measuring the fluorescence emitted from the stained oligonucleotide which is indicative of epitope detector bound to the surface and molecule expressing the selected epitope in the sample.

Applicants respectfully traverse this rejection.

Suzuki et al. (1995) disclose a method called double determinant immuno-polymerase chain reaction which utilizes two monoclonal antibodies, in which the antigens are sandwiched, and

a specific DNA molecule is used as marker. In this method, the first monoclonal antibody to bind the circulating antigen is immobilized. A biotinylated second monoclonal antibody is bound to the antigen and free streptavidin is used to attach a biotinylated DNA to the second monoclonal antibody. The biotinylated DNA complexed with antigen-antibody-streptavidin is amplified by PCR and the products then analyzed by Southern blot analysis.

As pointed out in the specification as filed, the method of Suzuki et al. is limited in that there is no direct correlation between the amount of signal and the amount of protein present, indicating that the method has limited value as a **quantitative** detection method. Although able to detect antigen with high sensitivity, the method of Suzuki et al. is not a quantitative tool.

In contrast, the method of the present invention is quantitative. In an earnest effort to advance the prosecution of this case and to clarify distinctions between the instant invention and the teachings of Suzuki et al., Applicants have amended claim 1 to be drawn to a method for quantifying molecules expressing a selected epitope in a sample. Support for this amendment can be found throughout the specification. See, for

example, page 4, line 28-30, page 5, line 18-20, page 9, line 29, 31 and page 10, line 24-26.

Further, the method of Suzuki et al., is used for DNA detection. As taught in Figure 1, at page 887 of Suzuki et al., the fluorescent compound ethidium bromide was used to locate DNA fragments in gel electrophoresis, and for staining the bound biotinylated DNA. In contrast, in the present invention, RNA is being quantified and fluorescence dyes which stain RNA are used. In an earnest effort to clarify this distinction, claim 1 has been amended to state that the amplified oligonucleotide is contacted with a fluorescent dye which binds to RNA directly and stains the oligonucleotide. Support for this amendment can be found in the specification at page 11, line 24, through page 12, line 3.

To anticipate a claim, the reference must teach all the elements of the claims. See MPEP § 2131. Since Suzuki et al. teaches neither a method for quantifying epitopes nor use of fluorescent dyes which stain RNAs, this reference cannot anticipate the claims as amended.

Withdrawal of this rejection under 35 U.S.C. § 102(b) is therefore respectfully requested.

V. Rejection of Claims 11-14 under 35 U.S.C. § 103(a)

Claims 11-14 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Suzuki et al. in view of Eberwine et al. and Zeytinoglu et al. The Examiner has acknowledged that Suzuki et al. does not teach step (d) of claim 11. However, the Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Suzuki et al. by adding an additional step which is a transcriptase based reaction as taught by Eberwine et al. and Zeytinoglu et al. The Examiner suggests that motivation to make this modification comes from Eberwine et al. which teaches that transcriptase based reaction is effective for the detection of rare messages and Zeytinoglu et al. which teaches that the PCR amplification method is advantageous where the amount of antigen is very small.

Accordingly, in an earnest effort to advance the prosecution and to clarify distinctions between the instant claimed invention and the prior art teachings, Applicants have amended step (d) of claim 11 in accordance with the teachings at page 10, lines 3-5, of the specification, to clarify that the amplified oligonucleotide is added to a reverse transcriptase based reaction or a replicase based reaction to increase sensitivity.

None of the cited prior art references teach this additional step.

MPEP § 2143 sets forth three criteria which must be met by the cited prior art combination to render an invention *prima facie* obvious. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations.

Since none of the prior art references cited teach an additional step of adding the amplified oligonucleotide to a reverse transcriptase based reaction or a replicase based reaction to increase sensitivity, the cited combination of art fails to teach or suggest all the limitations of the claims as amended. Thus, the cited combination of references fails to meet all the criteria required to render the instant claimed invention obvious.

Withdrawal of this rejection under 35 U.S.C. § 103 is therefore respectfully requested.

VI. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Pages have been attached hereto which show the changes made to the claims and specification and are labeled "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**".

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

At page 1, line 1, please replace the title with the following amended title:

--**Method of Detecting Molecules Expressing Selected Epitopes via Fluorescent Dyes**--

In the Claims:

1. A method for ~~detecting~~ quantifying molecules expressing a selected epitope in a sample comprising:

(a) immobilizing a molecule expressing a selected epitope in a sample to a selected surface;

(b) contacting the surface with an epitope detector so that the epitope detector binds to immobilized molecules on the surface, said epitope detector comprising an oligonucleotide attached to a monoclonal antibody for the selected epitope, a single chain Fv for the epitope or a constrained epitope specific CDR;

(c) amplifying the oligonucleotide of said epitope detector;

(d) contacting the amplified oligonucleotide with a fluorescent dye which binds to RNA directly and stains the oligonucleotide; and

(e) measuring fluorescence emitted from the stained oligonucleotide which is indicative of epitope detector bound to the surface and molecules expressing the selected epitope in the sample.

11. (amended) A method for detecting molecules expressing a selected epitope in a sample comprising:

(a) immobilizing a molecule expressing a selected epitope in a sample to a selected surface;

(b) contacting the surface with an epitope detector so that the epitope detector binds to immobilized molecules on the surface, said epitope detector comprising an oligonucleotide attached to a monoclonal antibody for the selected epitope, a single chain Fv for the epitope or a constrained epitope specific CDR;

(c) amplifying the oligonucleotide of said epitope detector;

(d) adding the amplified oligonucleotide of said epitope detector from step (c) to a reverse transcriptase based reaction or a replicase ~~and transcriptase~~ based reaction to

increase sensitivity;

(e) detecting the amplified oligonucleotide of said epitope detector from step (c).

12. (amended) The method of claim 11 wherein the amplified oligonucleotide of said epitope detector from step (c) is detected via contacting the amplified oligonucleotide of said epitope detector from step (c) with a fluorescent dye or probe which stains the oligonucleotide and measuring fluorescence emitted from the stained oligonucleotide which is indicative of epitope detector bound to the surface and molecules expressing the selected epitope in the sample.

13. The method of claim 11 further comprising quantifying the amplified oligonucleotide of said epitope detector from step (c) and detected in step (e).